Towards personalized treatment of rheumatic diseases with TNF inhibitors

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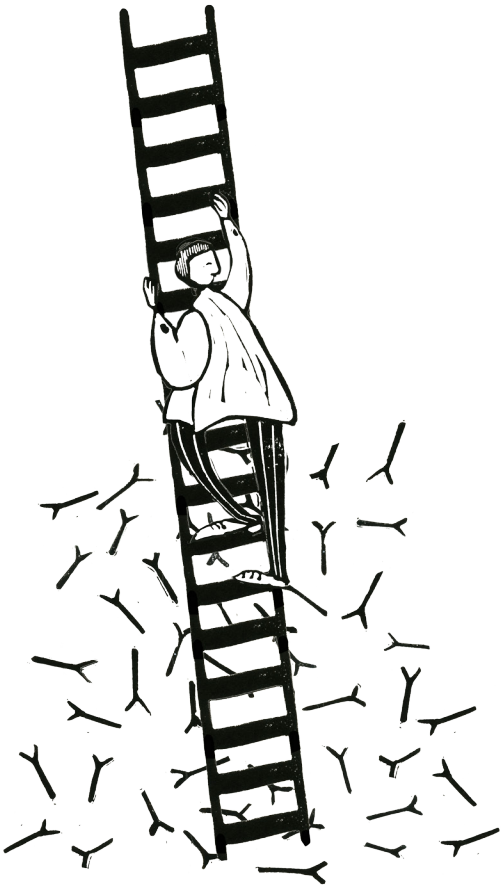
2020

document version
Publisher's PDF, also known as Version of record



Chapter 5

Interval prolongation in etanercept-treated patients with rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis: an open-label, randomised controlled trial

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ABSTRACT

Objectives The majority of patients with rheumatic diseases treated with etanercept may be overexposed to the drug. Data regarding etanercept tapering is scarce, particularly in psoriatic arthritis (PsA) and ankylosing spondylitis (AS). We compared a doubling of dose interval to continuation of the standard dose and subsequently studied the success rate of discontinuation of etanercept. Etanercept concentrations were measured throughout the study.

Methods 160 consecutive patients with rheumatoid arthritis (RA), PsA or AS with sustained minimal disease activity (MDA) were enrolled in this 18-month, open-label, randomised controlled trial. Patients in the intervention group doubled the dosing-interval at baseline and could discontinue etanercept 6 months later. In the control group, patients continued the standard dose up to 6 months, followed by doubling of the dosing-interval. All patients in MDA could discontinue etanercept after 12 months. Primary outcome was the proportion of patients maintaining MDA after 6 months follow-up.

Results At 6 months, MDA status was maintained in 47 (63%) patients in the intervention group and 56 (74%) in the control group (p=0.15), with similar results in each of the three rheumatic diseases. Median etanercept concentrations decreased from 1.50 μg/mL (25-75th percentile) 1.06-2.65) to 0.46 μg/mL (0.28-0.92) after 6 months of interval prolongation. In total, 50 patients discontinued etanercept, of whom 40% successfully with maintained MDA 6 months after discontinuation.

Conclusion As observed in RA, etanercept tapering can be safely attempted in PsA and AS patients in sustained MDA. In fact, a substantial proportion of patients could stop etanercept for at least 6 months. In many patients very low drug concentrations proved sufficient to control disease activity. On the other hand, the risk of minor and major flares is substantial, even in patients continuing standard dosing.

INTRODUCTION

Etanercept is a soluble recombinant tumor necrosis factor (TNF) receptor fusion protein targeting TNF, effective in the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS).[1-3] The approved standard-dose is 50mg every week or 25mg twice a week, but over the last few years studies (mostly in RA) have shown that lowering the dose of anti-TNF is feasible without loss of efficacy in a substantial proportion of patients in low disease activity state.[4-7]

It is, however, not yet possible to identify those patients who will flare on dose reduction. Dose reductions can potentially reduce blood drug levels too far, resulting in loss of effect but also increased immunogenicity.[8] Etanercept differs from the other two most frequently used TNF-inhibitors infliximab and adalimumab: it has a relatively short half-life in blood, and is rarely immunogenic.[9,10] In addition, data on etanercept dose reduction is scarce, particularly in PsA and AS.[11-15] Finally, there is little data about the success of reintroducing standard dose after a flare, but such knowledge is essential for patients considering a dose reduction.

In this pragmatic open label randomised controlled trial of RA, PsA and AS patients in minimal disease activity on etanercept, we compare the 6-month flare rate on dose-interval prolongation with that of standard dose continuation. Secondly, we study the proportion of patients who can subsequently discontinue their etanercept treatment. Thirdly, we relate flare rates to serum concentration of etanercept. Finally, we study the proportion of patients who regain MDA after flaring when standard dose is reintroduced.

METHODS

Study design and patients

This 18-month, open-label, randomised controlled study of a tapering-strategy with etanercept was performed at the Amsterdam Rheumatology and immunology Center, location Reade, The Netherlands. Patients with RA, PsA or AS (according to the American College of Rheumatology 1987 criteria, Classification of Psoriatic Arthritis (CASPAR) criteria and the 1984 New York Criteria, respectively), were included if they were on treatment with the standard dose of etanercept 50 mg subcutaneous (SC) weekly or 25 mg SC twice weekly for at least the previous 6 months. Another requirement for inclusion was that they fulfilled the minimal disease activity (MDA) criteria for at least 6 consecutive months.

The MDA criteria for each disease are detailed below. Every patient that did not fulfil the MDA criteria at some point in the study was classified as having a flare. Patients were excluded from the study if they had pre-planned reasons for treatment discontinuation. Clinical and laboratory assessments were scheduled at baseline and 3, 6, 9, 12, and 18 months thereafter. Etanercept concentrations were measured with an enzyme linked immunosorbent assay (ELISA) previously described in detail.[9] The study was approved by the Medical Research Ethics Committee of Slotervaart Hospital and Reade, and was conducted in accordance with the Declaration of Helsinki. The study was registered at the Dutch Trial Register (www.trialregister.nl), trial number NTR3903. Patients gave written informed consent.

MDA criteria

MDA criteria for RA was defined, according to the Outcome Measures in Rheumatology (OMERACT) MDA criteria, as a decision node: If tender joint count (TJC; 0-28)=0, swollen joint count (SJC; 0-28)=0 and erythrocyte sedimentation rate (ESR) ≤10 than the patients is considered to be in MDA. In all other cases a patient is considered to be in MDA if a score of at least 5 out of 7 from the following outcome measures is achieved: TJC (0-28) ≤1, SJC (0-28) ≤1, ESR ≤20, patient pain on visual analogue scale (VAS) ≤ 20 (scale 0-100), patient global disease activity VAS ≤ 20; Health assessment questionnaire (HAQ) score ≤ 0.5, physician global VAS ≤ 15. MDA in PsA has been developed in collaboration with Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA). MDA was defined as a score of at least 5 out of 7 from the following outcome measures: TJC (0-68) ≤1, SJC (0-66) ≤1, psoriasis area and severity index (PASI) ≤1, patient pain VAS ≤15, patient global disease activity VAS ≤ 20; HAQ score ≤0.5, and tender entheseal points ≤1(using Leeds Enthesitis Index; LEI). AS patients were in MDA in case Ankylosing Spondylitis Disease Activity Score (ASDAS), using C-reactive protein (CRP) <2.1.

Intervention

The 6-month randomised trial constituted the first study phase, where patients in the intervention group reduced the dose to 50% by doubling the dosing-interval and patients in the control group continued the standard dose. On flare, standard dose was reinstituted in the intervention group. In the second study phase patients in the intervention group could discontinue etanercept if they were still on reduced dose and met the MDA criteria; patients in the control group doubled the dosing-interval and could discontinue etanercept after 6 months if they were still on reduced dose and met the MDA criteria. Flares in the second phase were also treated with reinstitution of standard dosing. In total, all patients were followed up to 18 months. The design of the study is shown in the Figure S1. Concomitant disease-modifying antirheumatic drug (DMARD) or non-steroidal anti-inflammatory drug (NSAID) therapy was allowed and could be changed during follow-up.

Study outcomes

The primary study endpoint was the proportion of patients maintaining MDA in the 6-month randomised trial. Maintenance of MDA was defined as fulfilling MDA criteria at both 3 and 6 months, and at any unscheduled visits for a suspected flare. Secondary outcomes included the proportion of patients that increased or re-started the etanercept dose, and of those, the proportion that successfully regained MDA; and the proportion of patients that maintained MDA after 6 months of etanercept discontinuation. For this proportion, we combined the 6-month results of discontinuing patients from both randomisation groups. Etanercept concentrations throughout were also studied.

Randomisation

Patients were assigned in a 1:1 ratio to the intervention and control group. Randomisation was stratified according to disease and use of concomitant medication (concomitant use of methotrexate for RA and PsA and concomitant use of NSAID for AS). A randomisation list (Excel document) was managed by an independent co-worker of Reade and a backup independent co-worker, who were not otherwise involved in this trial. Investigators and other study staff had no access to the randomisation list. We aimed to include 150 patients in the study, since this number of patients was expected to be eligible in the study center. Table S1 explores several scenarios around an expected success (no-flare) rate of 0.7 to 0.9 in the control group compared to rates lowered by 0.1 to 0.3 in the intervention group.

Statistical analysis

Logistic regression analysed the difference in proportion of patients maintaining MDA at 6 months. Subsequently, an interaction term of disease (RA, PsA, AS) and study group (intervention or control) was included in the model. Unless otherwise indicated, analyses were by intention-to-treat. Because of uncertainty of expected flare rates and limitations in expected number of eligible patients, we decided against a noninferiority design, so differences between intervention and control groups were tested at a two-sided alpha level of 0.05. If MDA status was missing at a study visit, it was imputed by disease activity score of 28 joint count (DAS28)<2.6, disease activity of psoriatic arthritis (DAPSA)<14 or bath ankylosing spondylitis disease activity index (BASDAI)<4 for respectively RA, PsA and AS, where possible. Where such imputation was not possible, patients were excluded from analysis. A sensitivity analysis was performed with missing values classified as responder or all as non-responder. Patients were classified 'not in MDA' if they returned to the standard dose without a documented flare visit. Patients who returned to the standard dose while in MDA were censored and the event classified as protocol violation. In the intervention group, we compared median etanercept concentrations after 3 months of interval prolongation between those who maintained MDA during 6 months or not. In exploratory analysis, we investigated flares in more detail. For this, we described the change in disease activity at the moment a flare reported compared to baseline, according to change in DAS28, DAPSA and BASDAI for RA, PsA and AS respectively. Furthermore, we described disease activity at the moment of a flare in those who returned to standard dose or not. The threshold for statistical significance was set at $p<0.05$. For statistical analyses SPSS version 23.0 (SPSS, Chicago, IL) was used. Graphpad prism version 6 generated the figures.

RESULTS

Patients

Between June 2013 and May 2017, 380 consecutive patients were assessed for eligibility, of which 160 were enrolled and randomised (79 RA, 41 PsA, 40 AS; see trial profile in Figure 1). One RA patient was excluded from analysis, because she had already started dosing-interval prolongation before baseline visit. Four patients (1 RA, 3 AS) did not strictly meet the MDA criteria (Table S2). The treating rheumatologist agreed to prolong the dosing-interval in these patients. Patients had to meet the study criteria to maintain MDA as described in the methods section. The MDA-status of 5 other patients (2 RA, 1 PsA, 2 AS) could not be confirmed

at baseline due to incomplete data. These patients, however, did have minimal disease activity at baseline according to DAS28-ESR<2.6 for RA, DAPSA<14 for PsA, BASDAI<4 for AS and were included in the analysis.

Thus, 159 patients were included in the intention-to-treat analysis (baseline characteristics; Table 1A and 1B). Almost all patients received etanercept 50mg every week. Only five RA patients used 25mg twice a week, of which two were randomised to interval-prolongation at baseline. One RA patient prolonged the dosing-interval already at baseline while randomised to the control group. This patient was included in the control group in the ITT analysis. In total, 156 patients (98%) completed the 6-month trial, 132 patients (83%) completed 12 months follow-up and 116 (73%) completed 18 months of follow-up.

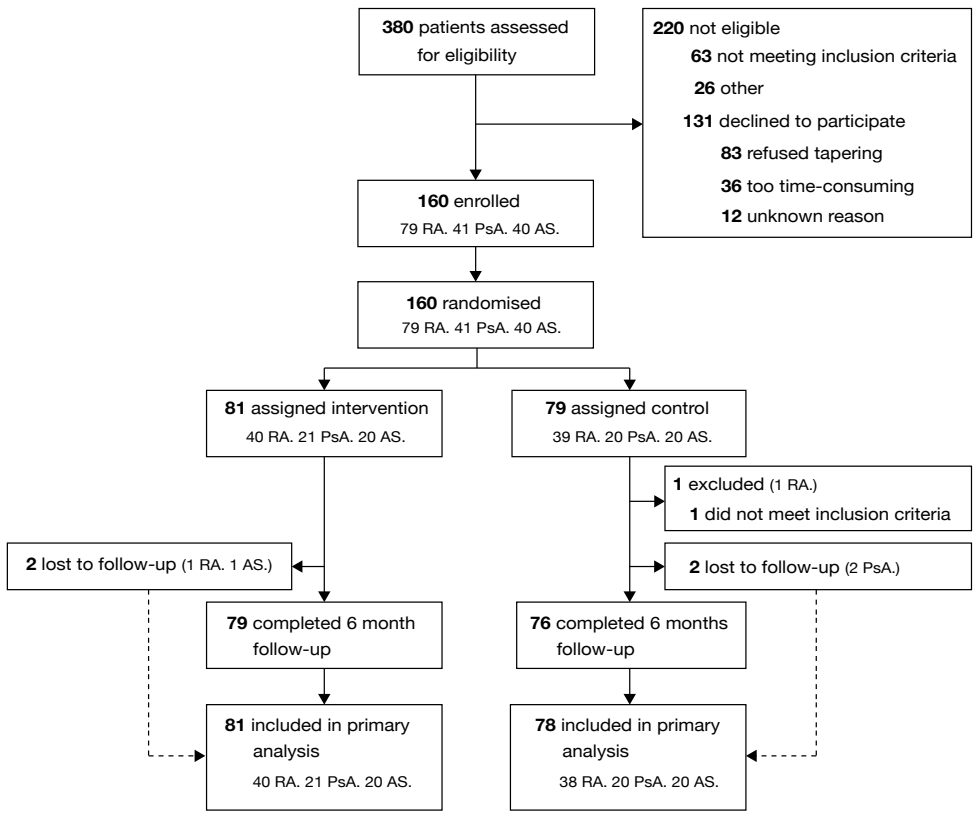

Figure 1. Trial profile up to 6 months follow-up for primary analysis. RA = rheumatoid arthritis; PsA = Psoriatic Arthritis; AS = Ankylosing Spondylitis.

Dosing-interval prolongation

Overall, MDA was maintained by 103 out of 151 patients during the first 6 months of follow-up, of which 47 (63%) in the intervention group and 56 (74%) in the control group (Relative risk was 0.83; p=0.15). A detailed flowchart is shown in Figure S2. Overall, mean time ± standard deviation (SD) to failure was 16 ± 7 weeks. In the intervention group time to failure was 18 ± 8 weeks and in the control group 14 ± 5 weeks from baseline.

MDA of 8 patients could not be imputed by the alternative criteria and were excluded from this analysis: 2 were lost to follow-up, 4 patients returned to standard dose while in MDA, 2 had incomplete MDA data. The results did not differ significantly between disease groups (no interaction effect, see supplement Table S3), and did not change significantly on (non)responder imputation of missing data (data not shown).

Less than half of the patients failing MDA returned to their standard dose in the intervention group (13 out of 28 patients; Figure S2). Mean time-to-return ± SD after baseline was 17 ± 8 weeks after baseline. Eight of these 13 patients achieved MDA again in the subsequent study visit. Four of the remaining patients and their rheumatologists were satisfied about the regained low disease activity although MDA was not achieved. The fifth patient (PsA) continued to have minor flares and switched to adalimumab. Also 10 patients out of the 15, who did not return to the standard dose, regained MDA again in follow-up. Four other patients continued the reduced dose in consultation with the rheumatologist. One patient discontinued etanercept. The control group that started interval prolongation at 6 months had slightly lower success rates at 12 months (for details see Supplemental Results and Figure S3). Exploratory analyses of flares after dosing-interval prolongation.

Patients failed MDA after dosing-interval prolongation, but also upon the standard dose in the 6-month randomised trial. At the time they failed MDA, disease activity was somewhat more deteriorated in patients prolonging dose-interval compared to standard-dosed treated RA and AS patients. In PsA, the difference was negligible (Table S4). Those patients in the intervention group who did not return to the standard dose after failing MDA seem to have milder flares, i.e. lower disease activity at the time they failed MDA (Table S5). Of note, reported number of patients are limited.

Table 1A. Demographics, DMARD therapy and disease status at baseline of patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis in the intervention or control study group.*

	RA		PsA		AS	
	IV	CO	IV	CO	IV	CO
Demographics	n= 40	n= 38	n= 21	n= 20	n= 20	n= 20
Age, mean ± SD (years)	57 ± 11	56 ± 12	50 ± 12	52 ± 13	47 ± 12	49 ± 10
Males	14 (35)	11 (29)	13 (62)	12 (60)	16 (80)	17 (85)
BMI, mean ± SD	26 ± 5	25 ± 3	26 ± 4	28 ± 4	26 ± 5	27 ± 4
DMARD therapy						
Etanercept treatment, median (25-75%; years)	4 (3-7)	5 (2-9)	6 (3-9)	6 (3-9)	5 (2-8)	8 (6-9)
MTX users	21 (52)	23 (60)	10 (48)	9 (45)	-	-
MTX dose, median (25-75%); mg/week)	15 (10-18)	15 (10-15)	13 (10-21)	13 (8-15)		
Prednisone users	1 (3)	4 (10)	0 (0)	0 (0)	0 (0)	1 (5)
NSAID users, median (25-75%);	-	-	-	-	8 (40)	6 (30)
Disease status						
Disease duration, median (25-75%; years)	12 (7-22)	12 (6-16)	9 (7-15)	10 (8-20)	15 (10-28)	17 (7-22)
History of Uveitis	-	-	-	-	8 (40)	9 (45)
HLA B27 positive	-	-	-	-	17 (85)	16 (80)
ACPA positive	28 (70)	22 (58)	-	-	-	-
IgM-RF positive	26 (65)	22 (58)	-	-	-	-
Erosive	27 (68)	19 (50)	9 (43)	6 (30)	-	-

*Numbers indicate count (%) unless otherwise indicated; SD = standard deviation; 25-75% = 25-75th percentiles. RA=rheumatoid arthritis; PsA=psoriatic arthritis; AS=ankylosing spondylitis; IV=intervention group; CO=control group; yrs=years, BMI=body mass index; DMARD=disease-modifying anti rheumatic drugs; MTX=methotrexate; NSAIDs=non-steroidal anti-inflammatory drugs; HLA=human leukocyte antigen; IgM-RF=IgM rheumatoid factor; ACPA=anti-citrullinated protein antibody.

Table 1B. Disease activity at baseline and after 6 months follow-up.*

	Intervention		Control	
	Baseline	6 months	Baseline	6 months
RA				
DAS28	1.6 ± 0.7	2.1 ± 0.9	1.7 ± 0.5	1.9 ± 0.7
Patient pain, mm	10 (3-16)	7 (3-28)	10 (4-18)	11 (3-25)
Patient global assessment, mm	10 (3-21)	10 (4-30)	12 (2-24)	10 (3-22)
Physician global assessment , mm	5 (2-10)	8 (3-14)	5 (2-11)	8 (3-15)
Swollen joint count (28)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Tender joint count (28)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
HAQ	0.5 (0.0-0.8)	0.5 (0.1-1.0)	0.3 (0.0-0.9)	0.3 (0.0-0.8)
ESR, mm/hour	5 (3-12)	12 (5-17)	5 (5-13)	8 (5-14)
CRP, mg/L	1 (1-3)	2 (1-3)	2 (1-3)	2 (1-4)
PsA				
DAS28	1.6 ± 0.7	1.8 ± 0.7	1.7 ± 0.7	1.8 ± 1.1
DAPSA	3 (1-4)	4 (1-10)	2 (0-3)	3 (0.7-8.4)
Patient pain, mm	8 (3-17)	9 (4-30)	5 (0-12)	5 (2-23)
Patient global assessment, mm	12 (2-18)	12 (5-42)	5 (1-19)	11 (2-28)
Physician global assessment , mm	4 (2-5)	6 (4-20)	4 (2-8)	6 (3-13)
Swollen joint count (66)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)
Tender joint count (68)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)

Table 1B. Continued.

	Intervention		Control	
	Baseline	6 months	Baseline	6 months
PsA				
LEI	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
PASI	0.0 (0.0-0.8)	0.0 (0.0-0.8)	0.0 (0.0-0.3)	0.0 (0.0-0.5)
HAQ	0.0 (0.0-0.5)	0.2 (0.0-0.4)	0.0 (0.0-0.3)	0.0 (0.0-0.4)
ESR, mm/hour	5 (2-9)	5 (3-14)	5 (3-20)	6 (2-17)
CRP, mg/L	1 (1-3)	1 (1-3)	1 (1-3)	2 (1-3)
AS				
ASDAS	1.3 ± 0.4	1.9 ± 0.9	1.4 ± 0.5	1.3 ± 0.6
BASDAI	1.6 ± 1.2	2.9 ± 2.1	1.9 ± 1.3	1.8 ± 1.6
BASFI	1.9 (0.4-2.9)	2.7 (0.4-4.3)	2.5 (1.1-3.3)	2.4 (1.0-5.3)
BASMI	2.9 (2.1-4.6)	2.6 (1.4-3.7)	1.6 (1.3-2.6)	2.6 (1.6-4.0)
ESR, mm/hour	5 (2-11)	5 (2-10)	5 (3-8)	5 (2-8)
CRP, mg/L	2 (1-3)	1 (1-5)	2 (1-2)	2 (1-3)

* results are mean ± standard deviation or median (25-75th percentile); DAS28=28-joints disease activity score; HAQ=health assessment questionnaire; ESR=erythrocyte sedimentation rate; CRP=C-reactive protein; DAPSA=disease activity in psoriatic arthritis; LEI=leeds enthesitis index; PASI=psoriasis area and severity index; ASDAS=ankylosing spondylitis disease activity score; BASDAI=bath ankylosing spondylitis disease activity index; BASFI=bath ankylosing spondylitis functional index ; BASMI=bath ankylosing spondylitis metrology index

Etanercept discontinuation

In total, 81 patients fulfilled MDA criteria 6 months after interval prolongation and were eligible for etanercept discontinuation (detailed flowchart; Figure S4). Forty-six of these patients actually discontinued etanercept in the study; the remaining 33 patients continued etanercept on the lower dose. Of these, 23 feared flares on discontinuation; the other 10 had other reasons such as rheumatologist reluctance and loss to follow up.

An additional 9 patients discontinued etanercept while strictly not meeting the criteria, however, the treating rheumatologist and patient decided to discontinue anyway. In total, five out of 55 patients could not be assessed because they were lost to follow-up (n=1), had incomplete MDA data (n=3) or returned to standard dose while in MDA (n=1). Of the 50 evaluable patients who discontinued, 20 (40%) maintained MDA up to six months after discontinuation. The other 30 lost MDA, of which 24 restarted etanercept. Mean ± SD time to restart of etanercept was 12 ± 6 weeks after treatment discontinuation. Seventeen of these patients regained MDA. Six other patients and their rheumatologists were also satisfied with the regained disease status, although MDA was not achieved or could not be determined.

Etanercept concentrations

In the per protocol analysis median (25-75th percentile) etanercept concentrations decreased from 1.50 μg/mL (1.06-2.65) to 0.48 μg/mL (0.29-0.78) after 3 months and 0.46 μg/mL (0.28-0.92) after 6 months of interval prolongation. Concentrations remained stable in the control group in the first 6 months; 1.59 μg/mL (1.09-2.11), 1.60 μg/mL (0.99-2.10), 1.50 μg/mL (0.96-2.22) at respectively, baseline, 3 and 6 months of follow-up (separated per disease; Figure 2). Patients in the intervention group who failed MDA had similar concentrations after 3 months of dosing-interval prolongation compared to those who maintained MDA, respectively, median (25-75th percentile) 0.55 (0.34-1.14) vs. 0.36 (0.27-0.78) μg/mL. patients who returned to standard dose before 3 months of follow-up were excluded for this analysis.

Three months after etanercept discontinuation, etanercept was undetectable in all patients. Intention-to-treat analyses per disease are shown in Figure S5. Of note, 8 patients had undetectable drug concentrations at baseline (n=5 intervention, n=3 control group), of which 5 had also undetectable concentrations at 3 months. One of the patients with undetectable drug concentrations at baseline and at 3 months lost MDA in the first 6 months. All other patients that lost MDA in the first 6 months had detectable drug concentrations after dosing-interval prolongation.

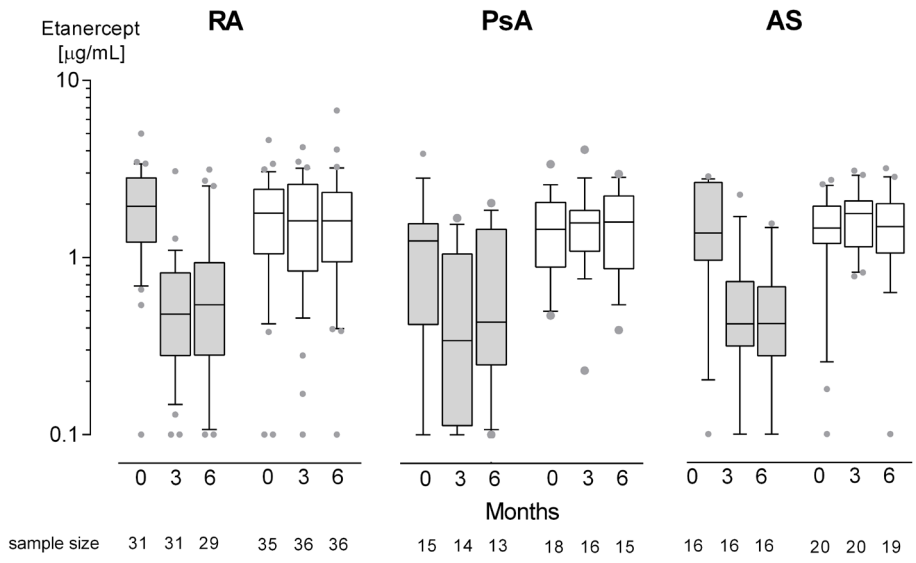

Figure 2. Median (boxplots; 25-75th percentile) etanercept concentrations (per protocol) during the first 6 months of follow-up in the intervention group (prolongation; gray boxplots) and the control group (continuation; white boxplots), separated by disease (RA, PsA, AS). Bars represent 10-90th percentile and outliers are shown separately (dots).

DISCUSSION

In this open-label, pragmatic, randomised trial, we found that the majority of PsA and AS patients, could successfully double the dosing-interval of etanercept for a period of at least 6 months, just like RA patients. Importantly, we confirmed that most patients with MDA loss can regain it under standard dose treatment. Of note, flare rates were lower, but still relatively high in patients continuing standard dosing. Dose reduction trials in RA and AS have reported success rates between the 44% and 87%.[11-15] We are aware of only one (cohort) study in PsA patients with a success rate of 72%.[13] Most studies have reduced the dose from 50mg to 25mg weekly. Our study showed that a more patient-friendly dosing-interval prolongation to 50mg once every two weeks results in similar success rates. Keeping the formulation the same is also more practical.

This is the first study to assess drug concentrations during tapering. All but one patient had detectable drug concentrations after interval prolongation, with amedian drug concentration around 0.5 µg/mL. Although little is known about the minimum necessary concentration, these results suggest a very low concentration is sufficient to control disease in the majority of patients once MDA is achieved. Of note, eight patients had undetectable drug concentrations at baseline suggesting non-adherence and drug-free remission.[16]

None of the patients stopping etanercept had detectable drug concentrations after 3 months. Forty percent of the patients remained off etanercept for at least to 6 months, in line with previous studies in RA (13–54%).[11,12,17] In PsA and AS, a few studies investigated discontinuation of several TNFi combined[18,19], but, to our knowledge, none investigated etanercept separately. Our result should be interpreted with caution, since only a subgroup of patients discontinued etanercept, and results per disease group were relatively small.

The study has limitations. A noninferiority design with a larger group of patients would have yielded more definite conclusions. In addition, the open-label design increased the risk of bias. For instance, patients and study staff may have been more focused on an increase of disease activity on dose reduction, resulting in an overestimation of the number of flares. Moreover, the lack of well-defined definition of flare criteria complicated the interpretation of successful tapering and discontinuation. It is important to differentiate between real flares and minor fluctuations in disease activity, and between flares caused by insufficient drug exposure and those due to insufficient drug effect despite adequate exposure (drug failure). Regarding the former, only half of the patients failing MDA returned to standard dose, suggesting their ‘flare’ was of minor impact, and several of these regained MDA regardless, similar to patients on standard dose temporarily losing MDA.

We conclude that, comparable to RA, etanercept tapering can be safely attempted in patients with PsA or AS. In many patients, very low drug concentrations proved sufficient to control disease activity. In fact, a substantial proportion of patients could stop etanercept for at least 6 months. On the other hand, the risk of minor and major flares is substantial, even in patients continuing standard dosing.

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SUPPLEMENTARY APPENDIX

METHODS

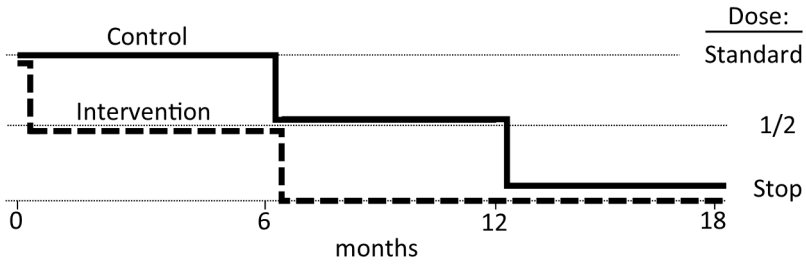

Figure S1. Study design; intervention group (dotted line) doubled dosing-interval at baseline and discontinued etanercept after 6 months follow-up. The control group continued the standard dose in first 6 months, followed by interval-prolongation and discontinuation.

Table S1. Several scenarios around an expected success rate of 0,7-0,9 in the control group compared to the intervention group.

			Risk difference		Risk ratio	
n	p1	p2	p1-p2	95% CI	p2/p1	95% CI
150	0.9	0.8	0.1	-0.01 – 0.21	0.89	0.78 – 1.02
		0.7	0.2	0.07 – 0.33	0.78	0.66 – 0.92
		0.6	0.3	0.16 – 0.44	0.67	0.55 – 0.81
	0.8	0.7	0.1	-0.04 – 0.24	0.88	0.73 – 1.05
		0.6	0.2	0.05 – 0.35	0.75	0.60 – 0.93
		0.5	0.3	0.15 – 0.45	0.63	0.48 – 0.80
	0.7	0.6	0.1	-0.05 – 0.25	0.86	0.68 – 1.09
		0.5	0.2	0.04 – 0.36	0.71	0.53 – 0.94
		0.4	0.3	0.14 – 0.46	0.57	0.42 – 0.78

n= sum of both groups; p1 = success rate in control group; p2 = success rate in intervention group; CI = confidence interval

RESULTS

Table S2. Disease activity of four patients not strictly meeting MDA criteria at baseline

1.	RA	DAS28-ESR	2.6
2.	AS	ASDAS	2.1
3.	AS	ASDAS	2.5
4.	AS	ASDAS	2.2

RA= rheumatoid arthritis; AS=Ankylosing Spondylitis; DAS28=disease activity score of 28 joint count; ESR=erythrocyte sedimentation rate; ASDAS= ankylosing spondylitis disease activity score

Dosing-interval prolongation after 6 months

Sixty-four out of 78 patients in the control group prolonged the interval at 6 months follow-up. Five patients prolonged the dosing-interval later in follow-up; one patient already started interval prolongation at baseline; 2 patients were lost to follow-up before 6 months; and six patients did not prolong the dosing-interval. In total, 33 out of 58 patients (53%) maintained MDA after dosing-interval prolongation up to 12 months follow-up. Two patients were lost to follow-up; one had protocol violation (returned while in MDA) and 3 other patients had missing data to determine whether MDA was maintained. Thirteen out of 25 patients who failed MDA returned to the standard dose. Eight of them achieved MDA again in the subsequent study visit. The other 5 patients and their rheumatologists were satisfied about the regained low disease activity. Of note, one patient in the control group, who started interval prolongation at baseline, also maintained MDA up to 6 months.

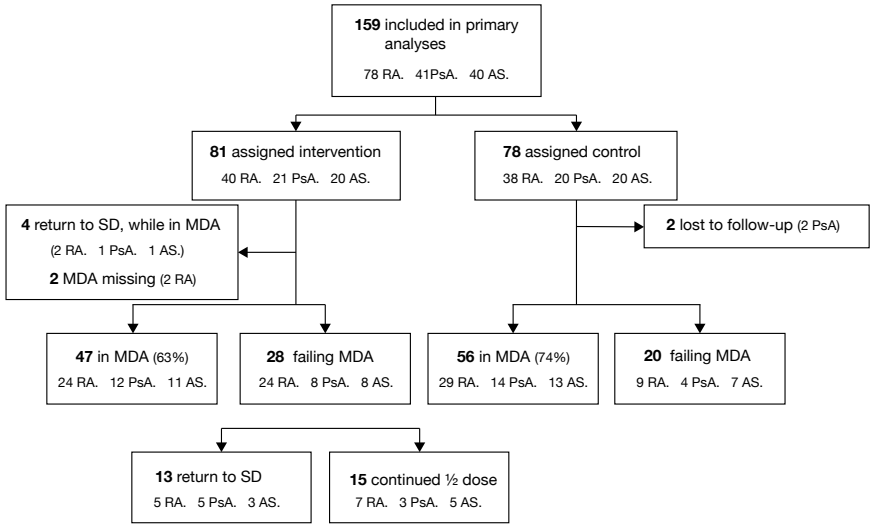

Figure S2. Flowchart of primary analysis (6-month trial phase) of patients maintaining MDA up to 6 months in both the intervention group and the control group. RA=rheumatoid arthritis; PsA=psoriatic arthritis; AS=ankylosing spondylitis; MDA=minimal disease activity; SD=Standard dose.

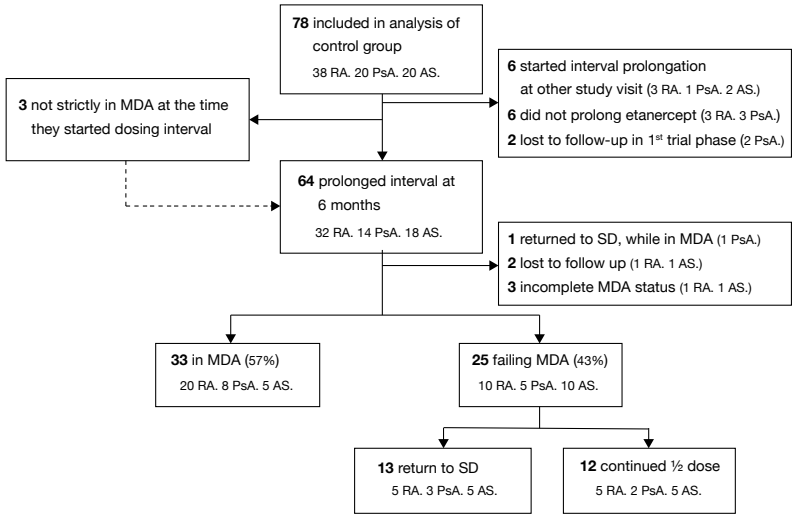

Figure S3. Flowchart of patients in the control group doubling the dosing-interval. RA=rheumatoid arthritis; PsA=psoriatic arthritis; AS=ankylosing spondylitis; MDA=minimal disease activity; SD=Standard dose.

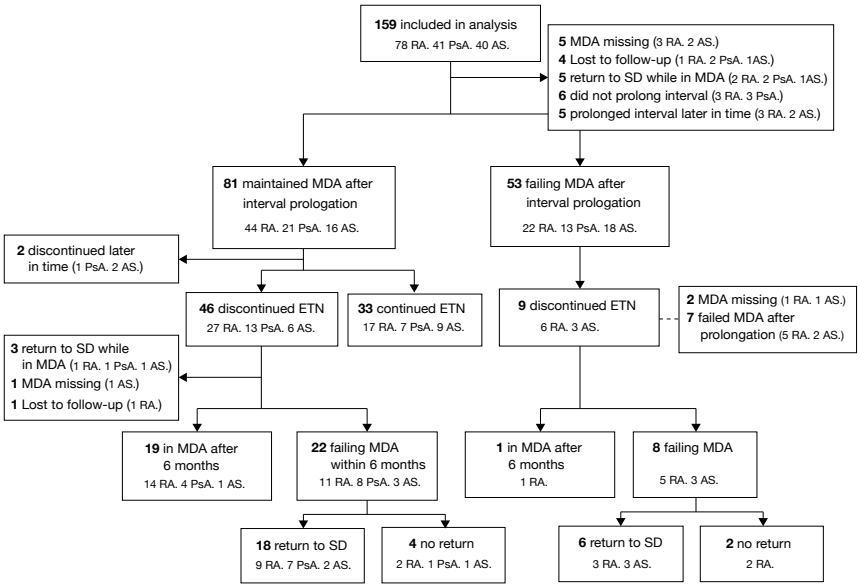

Figure S4. Flowchart of patients maintaining MDA following discontinuation of etanercept. RA=rheumatoid arthritis; PsA=psoriatic arthritis; AS=ankylosing spondylitis; MDA=minimal disease activity; SD=Standard dose; ETN=etanercept.

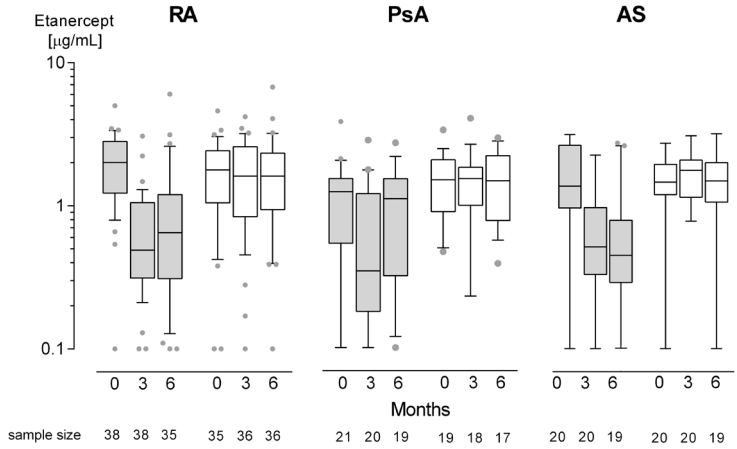

Figure S5. Median (boxplots; 25-75th percentile) etanercept concentrations (Intention-to-treat analysis) during the first 6 months of follow-up in the intervention group (prolongation; gray boxplots) and the control group (continuation; white boxplots), separated by disease (RA, PsA, AS). Bars represent 10-90th percentile and outliers are shown separately (dots).

Table S3. Proportion of patients who maintained MDA in the 6-month randomised trial separated per disease.*

	RA		PsA		AS	
Intervention	24/36	(67%)	12/20	(60%)	11/19	(58%)
Control	29/38	(76%)	14/18	(77%)	13/20	(65%)

*Numbers indicate count (%); RA= rheumatoid arthritis; PsA = psoriatic arthritis; AS=Ankylosing Spondylitis

Table S4. Change in disease activity after failing MDA compared to baseline.*

	Median ΔDAS28		Median ΔDAPSA		Median ΔASDAS	
Intervention	1,3 (0,7-1,5)	n=11	6,7 (5,6-9,3)	n=7	0,8 (0,2-1,6)	n=4
Control	0,9 (0,3-1,4)	n= 9	7,0 (-4,7-14,3)	n=4	0,6 (0,4-0,9)	n=7

* results are median (25-75th percentile); Δ= Delta; DAS28=disease activity score of 28 joint count; DAPSA=disease activity of psoriatic arthritis; ASDAS= ankylosing spondylitis disease activity score

Table S5. Disease activity at the time of a flare in the control group (CO) and intervention group (IV), divided by return to standard dose (SD) or no return (continuation of reduced dose).*

	Median DAS28		Median DAPSA		Median ASDAS	
IV - Return to SD	4,1 (2,9-1,5)	n=4	11,4 (9,0-18,2)	n=4	3,2 & 2,3	n=2
IV - No return	2,5 (2,4-3,5)	n=7	10,0	n=3	2,7 (2,4-3,0)	n=7
CO - Standard dose	3,1 (2,2-3,5)	n=9	9,7 (6,2-15,3)	n=4	2,5 (2,3-2,8)	n=7

* results are median (25-75th percentile); IV= intervention group; SD= standard dose; CO = control group; DAS28=disease activity score of 28 joint count; DAPSA=disease activity of psoriatic arthritis; ASDAS= ankylosing spondylitis disease activity score